DETAILED ACTION

Response to Amendment

Applicant's Amendment filed canceling claim 48, amending claims 16, 26, 27, 29, 30, 32, 35, 36, 38-41, 46, and 47 and adding the new claim 65, in the Response filed 27 December 2007 have been entered. Claims 49 and 59 remain withdrawn from consideration as drawn to a non-elected invention: neither requires a protease species having a naturally-occurring amino acid, or a relative insertion or deletion of an amino acid, at the subtilisin BPN'-correspondent position 62, according to claim 16. At page 17 of the Response filed 29 March 2006, Applicant affirmed the election of a protease comprising a naturally-occurring amino acid, or a relative insertion or deletion of an amino acid, at the subtilisin BPN'-correspondent position 62. The objection of record of claims 16 and 46 is withdrawn in view of Applicant's amendments to these claims. The amendment introduces no new matter where the substitution N269K is disclosed at page 12, line 3, and at page 54, line 17 of the specification. The amendment of claim 16 and cancellation of claim 48, overcome the rejection of record of claims herein for obviousness-type double patenting, which rejection is WITHDRAWN. The claim amendments remove the bases for the rejections of record of claims herein under 35 U.S.C. § 102, which are WITHDRAWN.

The prior art cited in the rejections under 35 U.S.C. §§ 102 and 103 in the communication mailed 28 June 2007 teaches many amino acid substitution positions that remain in the pending claims 16-26, 28, 30-34, 37-39, 41-47, 50-52, and are represented in the new claim 56. The substituents the prior art teaches at those positions remain in the claims. Subtilisins comprising such substitutions remain in the compositions of claims 53 and 54. While new grounds of rejection of claims 27, 29, 35, 36, and 40 under 35 U.S.C. §§ 102(b) and 103(a) are required by Applicant's claim amendments, further rejections stated below under 35 U.S.C. § 103(a) apply teachings of the prior art to the same substituents at the same positions previously rejected over the prior art cited in rejections made in the communication mailed 28 June 2007.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 16-18, 35, 50, 53, and 54 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Brode et al. US 6,475,765, made of record with the communication mailed 29 September 2005.

This new ground of rejection is necessitated by Applicant's amendment of claim 35. Brode et al. '765 disclose the preparation of many variant subtilisins DY, a sub-group I-S1 subtilase, comprising the substitutions N(62)[61]S/Q/D/E/P+G(160)[159]D where the positions numbered according the amino acid sequence of the mature subtilisin BPN' appear in parentheses and the corresponding position numbers in the sequence of the mature subtilisin DY appear in brackets, meeting limitations of claims 16-18, 35, and 50 herein. See cols. 3-5, 7-10, and Table 29.

The convention of representing subtilisin BPN' positions in parentheses and setting forth in brackets the corresponding positions in the amino acid sequences of other subgroup I-S1 and subgroup I-S2 subtilisins is maintained throughout the following rejections hereinbelow.

Brode et al. '765 disclose that their variant subtilisins DY are advantageously formulated in detergent compositions where they provide improved wash performance due to their "decreased absorption to, and increased hydrolysis of, an insoluble substrate" if used methods of cleaning textiles or surfaces, where such detergent compositions further comprise a surfactant and other enzymes, including "cellulases, lipases, amylases and [other] proteases", meeting limitations of claims 53 and 54 herein. See the abstract and cols. 83-100, particularly col. 86, lines 1-6.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived

Claims 16-18, 27, 28, 31, 32, 40-42, and 51-54 are rejected under 35 U.S.C. § 103(a) as being obvious over Brode et al. US 6,599,730, of record, and Ness et al. US 6,902,922, made of record herewith.

While this new ground of rejection is necessitated by Applicant's amendment of claims 27 and 40, in the interests of compact prosecution all substitutions taught by Ness et al. that are pertinent to the pending claims are cited and applied in this rejection. Brode et al. teach the preparation of variant subtilisins 309, a sub-group I-S2 subtilase, comprising the substitutions N(62)[61]S/Q/D/E/P and further teach that their variant subtilisins 309 provide improved wash performance when formulated in detergent compositions used in a method of cleaning textiles or surfaces and accordingly disclose preparation of detergent compositions comprising variant subtilisins 309, a surfactant and further enzymes including "cellulases, lipases, amylases and [other] proteases". See col. 8, line 38, through col. 11, line 44, the abstract, and cols. 97-10. Ness et al. teach the preparation of variant subtilisins 309 wherein a catalytic region is modified

to comprise one, or multiple, amino acid substitutions including any of I(72)[70]V, A(88)[86]V, H(120)[118]D, P(129)127]S, P(129)[127]D, S212[206]N, T(224)[218]S, and A(230)[224]V, as well as several other substitutions, e.g., the substitution N(76)[74]D now canceled from claim 27, in the catalytic region of subtilisin 309. See SEQ IDs NOs:130-261 and the formula at col. 2, lines 40-67. Ness et al. teach that their variant subtilisins 309 are advantageously formulated in detergent compositions that comprise surfactants and other enzymes including "cellulases, lipases, and the like", to provide improved "stain hydrolysis and solubilization". See col. 1, lines 42-54, and col. 5, lines 53-42.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin 309 variant according to claims 16-18, 27, 28, 31, 32, 40-42, 51, and 52 herein that comprise any of the N(62)[61]S/Q/D/E/P substitutions that Brode et al. teach are advantageously combined with other substitutions in subtilisin 309 and that further comprise one or more of the I(72)[70]V, A(88)[86]V, H(120)[118]D, P(129)127]S, P(129)[127]D, S212[206]N, T(224)[218]S, and A(230)[224]V substitutions that Ness et al. teach are advantageously combined with other substitutions in subtilisin 309, and obvious as well to such an artisan to prepare a cleaning or detergent composition according to claims 53 and 54 herein comprising such variant subtilisins 309. This is because Brode et al. and Ness et al. teach that each of their amino acid substitutions provide advantageous properties in a variant subtilisin 309, are advantageously combined with other modifications in a variant subtilisin 309 amino acid sequence, and that it is advantageous to prepare detergent compositions comprising such variant subtilisins, surfactants, and other enzymes including surfactants, and cellulases, lipases, and amylases. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 16-18, 24, 29, 34, 42, and 51-54 are rejected under 35 U.S.C. § 103(a) as being obvious over Brode et al. '730, of record, and Fanø et al. US 6,727,085, made of record herewith.

While this new ground of rejection is necessitated by Applicant's amendment of claim 29, in the interests of compact prosecution all substitutions taught by Fanø et al. that are pertinent to the pending claims are cited and applied in this rejection. The teachings of Brode et al., discussed above, of the preparation of variant subtilsins comprising the amino acid substitutions N(62)[61]S/Q/D/E/P and their advantageous incorporation in detergent compositions together with surfactants and lipases, amylases, and cellulases, are taken as before. Fanø et al. teach the preparation of variant subgroup I-S1 and I-S2 subtilisins wherein the substitution R(45)[43]K

is combined with other amino acid substitutions, the insertion L(96)[94]LA is combined with amino acid substitutions, the substitution T(143)[141]A is combined with other amino acid substitutions, and the substitution A(230)[224]V is combined with other amino acid substitutions. See Figure 1, cols. 6-8, col. 9, lines 15-62, col. 10, lines 1-22 and 64, and cols. 33 through 44. Fanø et al. further teach that their variant subgroup I-S1 and I-S2 subtilisins are advantageously formulated in detergent compositions comprising surfactants and other enzymes including, "a lipase, a cutinase, an amylase, a carbohydrase, a cellulase, a pectinase, a mannanase, an arabinase, a galacatanase, a xylanase, an oxidase . . . and/or a peroxidase", to provide more efficient degradation of protein stains wherein the protease inhibitors of egg whites are present, to which their variant subgroup I-S1 and I-S2 subtilisins are resistant. See cols. 20-29.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin 309 variant according to claims 16-18, 24, 29, 34, 42, and 50-52 herein that comprise any of the N(62)[61]S/Q/D/E/P substitutions that Brode et al. teach are advantageously combined with other substitutions in subtilisin 309 and that further comprise one or more of the R(45)[43]K substitution, L(96)[94]LA insertion, T(143)[141]A substitution, and A(230)[224]V substitution that Fanø et al. teach are advantageously combined with at least one further amino acid substitution in a variant subtilisin of either subgroup I-S1 or subgroup I-S2, and obvious as well to such an artisan to prepare a cleaning or detergent composition according to claims 53 and 54 herein comprising such variant subgroup I-S1 and subgroup I-S2 subtilisins. This is because Brode et al. and Fanø et al. teach that each of their amino acid substitutions, or insertion, provide advantageous properties in a variant subtilisin, are advantageously combined with other modifications in a variant subtilisin amino acid sequence, and that it is advantageous to prepare detergent compositions comprising such variant subtilisins, surfactants, and other enzymes including lipases, cutinases, amylases, carbohydrases, cellulases, pectinases, mannanases, arabinases, galacatanases, xylanases, oxidases, and peroxidases. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 16-18, 35, 36, 38 and 51-54 are rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Brode et al. '730, of record, and Weisgerber et al. US 6,566,115, made of record herewith.

While this new ground of rejection is necessitated by Applicant's amendment of claim 36, all substitutions taught by Weisgerber et al. that are pertinent to the pending claims are cited and applied in this rejection in the interests of compact prosecution. The teachings of Brode et al.,

discussed above, of the preparation of variant subtilisins, including subtilisin 309, comprising the amino acid substitutions N(62)[61]S/Q/D/E/P, as well as their advantageous incorporation in detergent compositions together with other enzymes such as lipases and cellulases are taken as before. Weisgerber et al. teach the preparation of variant subgroup I-S1 and subgroup I-S2 subtilisins, such as "subtilisin BPN', subtilisin Carlsberg, subtilisin DY, [and] subtilisin 309", by making substitutions of cysteine for any amino acid present at one or more of the subtilisin BPN'-correspondent positions "158 . . . 163 [and] 186", wherein such starting subtilisins may already comprise prior art amino acid modifications at one or more subtilisin BPN' correspondent positions including 21, 22, 24, 32, 33, 36, 45, 48-50, 64, 67, 87, 94, 95, 101-105, 107, 109, 110, 123, 124, 126-129, 135, 152, 155, 156, 166, 169-172, 189, 195, 197, 199, 204, 206, 210, 213-218, 221, 222, 260, 265, and 274, in order to protect persons using such variant subtilisins, wherein inert polymers are conjugated to the one or more cysteine substituents, from an immunogenic response due to contact with the variants when the variants are incorporated in cleaning and detergent compositions. See col. 2, line 19, through col. 6, line 39. Weisgerber et al. teach that their variant subgroup I-S1 and subgroup I-S2 subtilisins are advantageously added to detergent compositions, together with other enzymes such as amylases, cellulases and lipases. See col. 17 through col. 21.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare variant subtilisins that comprise any of the N(62)[61]S/Q/D/E/P substitutions that Brode et al. teach are advantageously combined with other substitutions in variant subtilisins and that further comprise any the A(158)[156]C, S(163)[158]C, or R(186)[180]C substitutions that Weisgerber teach are advantageously combined with at least one further amino acid substitution in preparing variant subgroup I-S1 and subgroup I-S2 subtilsins that reduce the risk of immunogenic exposure for consumers, according to claims 16-18, 35, 36, 38 and 50-52 herein, and obvious as well to such an artisan to prepare a cleaning or detergent composition according to claims 53 and 54 herein comprising such variant subgroup I-S1 and subgroup I-S2 subtilisins. This is because both Brode et al. and Weisgerber et al. teach that each of their amino acid substitutions provide advantageous properties in a variant subtilisin, are advantageously combined with other modifications in a variant subtilisin amino acid sequence, and that it is advantageous to prepare detergent compositions comprising such variant subtilisins, surfactants, and other enzymes including additional enzymes, including cellulases, amylases, and lipases. While Weisgerber et al. perform additional modifications of subtilisin variants, neither the pending claims nor the specification exclude further modification of a protease variant. Based upon the teachings of the cited references, the level of skill of one

of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 16-19, 25, 26, 30, 31, 33, 34, 42, 46, and 51-54 remain rejected, essentially for reasons of record, under 35 U.S.C. § 103(a) as being obvious over Brode et al., discussed above, in view of Christianson et al., US 5,340,735, of record.

Applicant's arguments at pages 16 and 17 of the Response filed 27 December 2007 have been fully considered but they are not persuasive. This is essentially the rejection of record addressing subject matter indicated as obvious over the prior art publications cited at pages 10 and 11 of the communication mailed 28 June 2007. The teachings of Brode et al. of preparation of variant subtilsins comprising any of the amino acid substitutions N(62)[61]S/Q/D/E/P and their advantageous incorporation in detergent compositions together with surfactants and lipases, amylases, and cellulases, discussed above, are taken as before. Christianson et al. teach that structurally stabilizing amino acid substitutions in the amino acid sequence of a subgroup I-S2 subtilisin will increase its shelf stability and sustain its catalytic activity in detergent compositions, primarily by enhancing van der Waals interactions in the interior regions. See col. 1, at lines 40-56, and col. 19, line 22, through col. 20, line 24. In view of their definitions of "small, hydrophobic amino acid" and "small amino acid" at lines 45-56 of col. 8, Christianson et al. teach the preparation of subtilisin variants comprising the substitutions S(3)[3]T, S(3)[3]A, V(4)[4]A, A(48)[47]T, T(71)[69]A, N(116)[114]S, H(120)[118]N, H(120)[118]D, H(120)[118]Q, H(120)[118]K, H(120)[118]E, H(120)[118]Y, H(120)[118]S, S(132)[130]T, S(132)[130]G, T(143)[141]A, A(230)[224]V, and T(274)[268]A. See col. 8, line 49, through col. 10, line 4.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a variant subgroup I-S2 subtilisin, including a variant subtilisin 309, that comprises any one of the substitutions at the subtilisin BPN'-correspondent position 62 taught Brode et al. that further comprises one or more of the S(3)[3]T, S(3)[3]A, V(4)[4]A, A(48)[47]T, T(71)[69]A, N(116)[114]S, H(120)[118]N, H(120)[118]D, H(120)[118]Q, H(120)[118]K, H(120)[118]E, H(120)[118]Y, H(120)[118]S, S(132)[130]T, S(132)[130]G, T(143)[141]A, A(230)[224]V, and T(274)[268]A substitutions taught by Christianson et al. according to claims 16-19, 25, 26, 30, 31, 33, 34, 42, 46, 51, and 52 herein, and obvious as well to such an artisan to prepare a detergent composition according to claims 53 and 54 herein. This is because Brode et al. teach the advantages of their amino acid N(62)[61]S/Q/D/E/P substitutions at the BPN'-correspondent position 62 in a subtilisin, because asparagine is present at the subtilisin BPN'-correspondent position 62 in the sub-group I-S2 subtilases of both Brode et al. and Christianson et al., and because Christianson et al. teach that any of their structurally-stabilizing

amino acid substitutions will increase the shelf stability of a variant sub-group I-S2 subtilase, and sustain its catalytic activity, in detergent compositions. It would have also have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a cleaning or detergent composition of claims 53 and 54 herein because both Brode et al. and Christianson et al. suggest that sub-group I-S2 subtilases modified according to their teachings are particularly effective in detergent compositions and because Brode et al. teach that such detergent and cleaning compositions advantageously comprise a surfactant as well as other enzymes such as amylases, lipases, cellulases, and other proteases. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 16-20, 22-24, 26, 30, 32, 37, 38, 39, 41-45, 47, and 50-54 remain rejected, essentially for reasons of record, under 35 U.S.C. § 103(a) as being obvious over Brode et al., discussed above, Gosselink et al. US 6,121,226, and any of Ballinger et al. US 5,741,664, US 5,780,285, or US 5,837,516, in view of Ghosh et al. US 6,376,450, all made of record with the communication mailed 29 September 2007.

Applicant's arguments at pages 16 and 17 of the Response filed 27 December 2007 have been fully considered but they are not persuasive. This is essentially the rejection of record addressing subject matter indicated as obvious over the prior art publications cited at pages 13 and 14 of the communication mailed 28 June 2007. In the interests of compact prosecution all sites for substitutions taught by Gosselink et al. pertinent to the pending claims, and all of the substituents in substitutions at the positions of Gosselink et al. taught by Ghosh et al. pertinent to the pending claims, are cited and applied in this rejection.

The teachings of Brode et al., discussed above, of the preparation of variant subtilsins comprising the amino acid substitutions N(62)[61]S/Q/D/E/P and their advantageous incorporation in detergent compositions together with surfactants and lipases, amylases, and cellulases, are taken as before. Ballinger et al. teach the modification of the sub-group I-S1 subtilisin BPN' having the amino acid sequence set forth in SEQ ID NO:1 herein by replacing an asparagine at position 62 with aspartate or glutamate to alter its native specificity for hydrophobic, or small, uncharged, amino acids, providing variants with a higher degree of specificity for cleavage at basic amino acid residues. See col. 2, line 66, to col. 3, line 16 and claims 1 and 2 of Ballinger et al. '664. While Gosselink et al. do not specifically disclose the preparation of variant subtilisins, they teach the preparation of detergent compositions that comprise a surfactant and any of several enzymes, such as amylases, lipases, cellulases, and

peroxidases, which further comprise variant subtilisins having an amino acid substitution that replaces any amino acid present in any subtilisin at a position corresponding to position 62 of the mature subtilisin BPN', a class I-S1 subtilase having the amino acid sequence of SEQ ID NO:1 herein, with aspartate. Gosselink et al. further teach that amino acid substitutions in either a sub-group I-S1 subtilase, such as subtilisin BPN', or a sub-group I-S2 subtilase, such as subtilisin 309, may be combined with one another when made at positions that include the subtilisin BPN'-correspondent positions 1, 3, 4, 8, 9, 10, 13, 16, 17, 18 19, 20, 21, 22, 24, 27, 38, 43, 48, 55 57, 61, 72, 75, 76, 77, 78, 87, 101, 111 114, 116, 119, 121, 128, 130, 133, 134, 137, 140; 158, 160, 167, 174, 183, 184, 185, 188, 192, 203; 204, 212, 213, 222, 224, 228, 230, 237, 238, 240 242, 244, 251, 254, 255, 256, 257, 258, 259, 260 261, 262, 263, 265, 268, 269, 271, and 274. See cols. 27-31, particularly col. 29 at lines 38-67 and col. 30 at line 31 through col. 31 at line 4. The positions taught for substitution by Gosselink et al. now cited herein is reduced relative to those cited in the communication mailed 28 June 2007 to reflect the cancellations of some positions in the amended claims filed 27 December 2007.

Ghosh et al. teach the preparation of multiply-substituted variant subgroup I-S1 and subgroup I-S2 subtilisins comprising the amino acid substitution N62D and comprising as well one or more of the substitutions S3L, V4E, I8V, R10H, N18S, G20A, G20R, T22K, K27R, N43D, P55S, S57P, G61E, A114V, N116D, N116S, S130T, N140D, N173D, A174V, N183D, N184S, N184D, N185D, N185S, V203A, N204T, N204D, Q206L, N218S, N218D, M222S, T224A, A230V, V244A, V244I, K251R, K251T, K251R, K251Q, T255S, S256N, S259G T260R, T260A, N261D, and L262S where all of these positions are expressly numbered by correspondence with the amino acid sequence of subtilisin BPN'. See Table II at cols. 17-30. Ghosh et al. further teach that variant subgroup I-S1 and I-S2 subtilisins comprising one or more of these substitutions are advantageously added to cleaning compositions, including detergent compositions, to "provid[e] improved and enhanced cleaning of fabrics, dishware, tableware, kitchenware, cookware, and other hard surface substrates". See col. 4, lines 45-53, and col. 65, line 1, through col. 108, line 50.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin variant comprising any among the substitutions taught by Brode et al., which include those taught by Ballinger et al., in a subgroup I-S1 subtilisin such as subtilisin BPN', or in a subgroup I-S2 subtilisin such as subtilisin 309, and to further introduce one or more of the amino acid substitutions S3L, V4E, I8V, R10H, N18S, G20A, G20R, T22K, K27R, N43D, P55S, S57P, G61E, A114V, N116D, N116S, S130T, N140D, N173D, A174V, N183D, N184S, N184D, N185D, N185S, V203A, N204T, N204D, Q206L, N218S, N218D, M222S,

T224A, A230V, V244A, V244I, K251R, K251T, K251R, K251Q, T255S, S256N, S259G T260R, T260A, N261D, and L262S taught by Ghosh et al. in a variant subgroup I-S1 or subgroup I-S2 subtilisin according to claims 16-20, 22-24, 26, 30, 32, 37, 38, 39, 41-45, 47 and 50-52 herein, where the claim 47 alternatively describes the substitution R10H+N62D, and obvious as well to prepare a detergent composition comprising such a variant subtilisin of claims 53 and 54 herein. This is because Ballinger et al. and Brode et al. teach the advantages of amino acid substitutions of any of serine, aspartate, proline, glutamine, or glutamate for an asparagine present at the BPN'-correspondent position 62 in a subtilisin, because asparagine is present at the subtilisin BPN'-correspondent position 62 in both sub-group I-S1 subtilases and sub-group I-S2 subtilases, because Ghosh et al. teach that each of their many amino acid substitutions are both individually advantageous as well as advantageously combined with one or more further amino acid substitutions in a subtilisin, because Gosselink et al. teach that combining several worthwhile amino acid substitutions was the state of the art of subtilisin modification at the time the invention was made, and because Brode et al. and Ghosh et al. show that a substitution at the subtilisin BPN'-correspondent position 62 was considered to be advantageously combined with further amino acid substitutions in modifying a subtilisin to make it more effective for use in detergent compositions at the time the invention was made. It would have also have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a cleaning or detergent composition of claims 53 and 54 herein because Brode et al. '730 and '756, Gosselink et al., and Ghosh et al. all teach that such multiply-substituted subtilisins are advantageously added to detergent and cleaning compositions together with other enzymes such as amylases, lipases, cellulases, and other proteases. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 16, 21-23, 25, 31, 32, 34, 39, 42, 43, 46, 50-54, remain rejected, and the new claim 56 is now rejected, essentially for reasons of record, under 35 U.S.C. § 103(a) as being obvious over Brode et al., Gosselink et al. and Ballinger et al., discussed above, in view of Aaslyng et al. US 5,665,587, made of record with the communication mailed 29 September 2007.

Applicant's arguments at pages 16 and 17 of the Response filed 27 December 2007 have been fully considered but they are not persuasive. This is essentially the rejection of record addressing subject matter indicated as obvious over the prior art publications cited at pages 8-10 of the communication mailed 28 June 2007. In the interests of compact prosecution all sites for substitutions taught by Gosselink et al. pertinent to the pending claims, and all of the

substituents in substitutions at the positions of Gosselink et al. taught by Aaslyng et al. pertinent to the pending claims, are cited and applied in this rejection.

The teachings of Brode et al., discussed above, of the preparation of variant subtilsins comprising the amino acid substitutions N(62)[61]S/Q/D/E/P and their advantageous incorporation in detergent compositions together with surfactants and lipases, amylases, and cellulases, are taken as before, as are the teachings of Ballinger et al. of N(62)[61]D/E substitutions in a variant subtilisin to alter substrate specificity, discussed above, and the teachings of Gosselink et al. of preparation of detergent compositions comprising a surfactant and any of several enzymes, such as amylases, lipases, cellulases, and peroxidases, which further comprise variant subtilisins having one or more amino acid substitutions at over 78 positions in any subtilisin, including those cited in the preceding rejection such as the position corresponding to position 62 of the mature subtilisin BPN'.

Aaslyng et al. teach the preparation of variant subtilisins comprising one or more amino acid substitutions including P14D, P14K, T22K, K27R, V51D, H120D, H120K, P129D, N140D, N140K, G195E, K237R, K251E, K251R, and S265R where these positions are identified by correspondence with the amino acid sequence of the mature subtilisin BPN'. See cols 19-21, col. 42 at line 47, and claim 1. Aaslyng et al. further teach that each of these substitutions may be made either in a sub-group I-S1 subtilisin or a sub-group I-S2 subtilisin and that, whether they are made singly or in combination with other amino acid substitutions, will provide a variant subtilisin advantageously formulated in detergent compositions because the variant will have an isoelectric point shifted to achieve an optimum wash performance by matching the pH of the wash liquor comprising the detergent composition wherein the variant "is intended for use". See col. 18 al lines 6-16.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin variant comprising any among the substitutions taught by Brode et al., which include those taught by Ballinger et al., in a subgroup I-S1 subtilisin such as subtilisin BPN', or in a subgroup I-S2 subtilisin such as subtilisin 309, and to further introduce one or more of the amino acid substitutions P14D, P14K, T22K, K27R, V51D, H120D, H120K, P129D, N140D, N140K, G195E, K237R, K251E, K251R, and S265R taught by Aaslyng et al., according to claims 16, 21-23, 25, 31, 32, 34, 39, 42, 43, 46, and 50-52, as well as to make a variant subtilisin comprising any of the N(62)[61]S/Q/D/E/P+K(237)[231]R substitutions of new claim 56, and to prepare a detergent composition comprising such a variant subtilisin of claims 53 and 54 herein. This is because Ballinger et al. and Brode et al. teach the advantages of amino acid substitutions of any of serine, aspartate, proline, glutamine, or glutamate for an asparagine

present at the BPN'-correspondent position 62 in a subtilisin, because asparagine is present at the subtilisin BPN'-correspondent position 62 in both sub-group I-S1 subtilases and sub-group I-S2 subtilases, because Aaslyng et al. teach that the net molecular charge-altering substitutions, whether made individually or in sets of substitutions, will shift the isoelectric point of a variant subtilisin that comprises one or more of them in order to achieve an optimum wash performance of variant at any target pH of the wash liquor wherein its use is intended, because Gosselink et al. teach that combining several worthwhile amino acid substitutions was the state of the art of subtilisin modification at the time the invention was made, and because Brode et al. teach that a subtilisin is advantageously modified to make it more effective for use in detergent compositions by combining a substitution at the subtilisin BPN'-correspondent position 62 with other amino acid substitutions at the time the invention was made. It would have also have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a cleaning or detergent composition of claims 53 and 54 herein because Brode et al., Gosselink et al., and Aaslyng et al. all teach that such multiply-substituted subtilisins are advantageously added to detergent and cleaning compositions together with other enzymes such as amylases, lipases, cellulases, and other proteases. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 16-18, 26, 37, 39, 41, and 50-54 remain rejected, essentially for reasons of record, under 35 U.S.C. § 103(a) as being obvious over Brode et al., Gosselink et al. and Ballinger et al., discussed above, in view of Sierkstra et al., US 5,837,517, made of record with the communication mailed 29 September 2007.

Applicant's arguments at pages 16 and 17 of the Response filed 27 December 2007 have been fully considered but they are not persuasive. This is essentially the rejection of record addressing subject matter indicated as obvious over the prior art publications cited at pages 12 and 13 of the communication mailed 28 June 2007. In the interests of compact prosecution all sites for substitutions taught by Gosselink et al. pertinent to the pending claims, and all of the substituents in substitutions at the positions of Gosselink et al. taught by Sierkstra et al. pertinent to the pending claims, are cited and applied in this rejection.

The teachings of Brode et al., discussed above, of the preparation of variant subtilsins comprising the amino acid substitutions N(62)[61]S/Q/D/E/P and their advantageous incorporation in detergent compositions together with surfactants and lipases, amylases, and cellulases, are taken as before, as are the teachings of Ballinger et al. of N(62)[61]D/E substitutions in a variant subtilisin to alter substrate specificity, discussed above, and the

teachings of Gosselink et al. of preparation of detergent compositions comprising a surfactant and any of several enzymes, such as amylases, lipases, cellulases, and peroxidases, which further comprise variant subtilisins having one or more amino acid substitutions at over 78 positions in any subtilisin, including those cited in the preceding rejection such as the position corresponding to position 62 of the mature subtilisin BPN'. Sierkstra et al. teach that introducing one or more of the substitutions S(57)[55]P, H(120)[118]D, G(195)[189]E, M(222)[218]A, and M(222)[218]S in a subtilisin amino acid sequence, where these substitutions are numbered by correspondence with the amino acid sequence of subtilisin BPN', will increase its wash performance and/or stability in a detergent composition. See the abstract and the patent claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin variant comprising any among the substitutions taught by Brode et al., which include those taught by Ballinger et al. in a subgroup I-S1 subtilisin such as subtilisin BPN', or in a subgroup I-S2 subtilisin such as subtilisin 309, and to further introduce one or more of the amino acid substitutions S(57)[55]P, H(120)[118]D, G(195)[189]E, M(222)[218]A, and M(222)[218]S taught by Sierkstra et al. according to claims 16-18, 26, 37, 39, 41, 51, and 52, and to prepare a detergent composition comprising such a variant subtilisin of claims 53 and 54 herein. This is because Ballinger et al. and Brode et al. teach the advantages of amino acid substitutions of any of serine, aspartate, proline, glutamine, or glutamate for an asparagine present at the BPN'-correspondent position 62 in a subtilisin, because asparagine is present at the subtilisin BPN'-correspondent position 62 in both sub-group I-S1 subtilases and sub-group I-S2 subtilases, because Sierkstra et al. teach that each of further their stabilizing amino acid substitutions S(57)[55]P, H(120)[118]D, G(195)[189]E, M(222)[218]A, and M(222)[218]S will provide a variant subtilisin with an increased wash performance and/or stability in a detergent composition. It would have also have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a cleaning or detergent composition of claims 53 and 54 herein because Brode et al., Gosselink et al., and Sierkstra et al. all teach that such multiply-substituted subtilisins are advantageously added to detergent and cleaning compositions together with other enzymes such as amylases, lipases, cellulases, and other proteases. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Claims 16-18, 28, and 50-54 remain rejected, essentially for reasons of record, under 35 U.S.C. § 103(a) as being obvious over Brode et al.., Ballinger et al. and Gosselink et al.,

discussed above, in view of Bott et al., US 5,700,676, all made of record with the communication mailed 29 September 2007.

Applicant's arguments at pages 16 and 17 of the Response filed 27 December 2007 have been fully considered but they are not persuasive. This is essentially the rejection of record addressing subject matter indicated as obvious over the prior art publications cited at pages 14 and 15 of the communication mailed 28 June 2007. The teachings of Brode et al., discussed above, of the preparation of variant subtilsins comprising the amino acid substitutions N(62)[61]S/Q/D/E/P and their advantageous incorporation in detergent compositions together with surfactants and lipases, amylases, and cellulases, are taken as before, as are the teachings of Ballinger et al. of N(62)[61]D/E substitutions in a variant subtilisin to alter substrate specificity, discussed above, and the teachings of Gosselink et al. of preparation of detergent compositions comprising a surfactant and any of several enzymes, such as amylases, lipases, cellulases, and peroxidases, which further comprise variant subtilisins having one or more amino acid substitutions at over 78 positions, including the subtilisin BPN'-correspondent positions 62 and 87, in any subtilisin. Bott et al. teach the preparation of the amino acid substitution S(87)[85]C in the amino acid sequence of subtilisin BPN' to form a disulfide bond between the positions 24 and 87 and thereby increase both its thermal stability and resistance to autocatalytic cleavage. See Example 11 at cols. 67-70, where this substitution pair provides improved stability and nearly equivalent autocatalytic cleavage characteristics by comparison with the native, or wild-type, subtilisin BPN'.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a subtilisin variant comprising any of the substitutions taught by Brode et al., which include those taught by Ballinger et al., in a subgroup I-S1 subtilisin such as subtilisin BPN', or in a subgroup I-S2 subtilisin such as subtilisin 309, and to further introduce the substitution S(87)[85]C taught by Bott et al. according to claims 16-18, 28, and 50-52, and to prepare a detergent composition comprising such a variant subtilisin of claims 53 and 54 herein. This is because Ballinger et al. and Brode et al. teach the advantages of amino acid substitutions of any of serine, aspartate, proline, glutamine, or glutamate for an asparagine present at the BPN'-correspondent position 62 in a subtilisin, because asparagine is present at the subtilisin BPN'-correspondent position 62 in both sub-group I-S1 subtilases and sub-group I-S2 subtilases, and because Bott et al. teach that their S(87)[85]C substitution will provide a variant subtilisin with increased stability and resistance to autocatalytic cleavage. It would have also have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a cleaning or detergent composition of claims 53 and 54 herein because Brode et al.,

Gosselink et al., and Sierkstra et al. all teach that such multiply-substituted subtilisins are advantageously added to detergent and cleaning compositions together with other enzymes such as amylases, lipases, cellulases, and other proteases. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashaat T. Nashed/
Nashaat T. Nashed, Ph.D.
Supervisory Primary Examiner
Art Unit 1652

/William W. Moore/
22 March 2008